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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,199	12/20/2001	Norbert Maurer	INEX.P-005	6234

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/019,199	MAURER ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on 9-26-03 is acknowledged.

Claims included in the prosecution are 13-32.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 13-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hope (6,447,800) in view of Wheeler (5,976,567) or WO 98/51278 of record.

Hope discloses a method of preparation of liposomes containing a variety of active agents. The method involves combining already formed liposomes with an active agent and organic solvent, ethanol (at least 10 %), allowing a certain amount of time and diluting the organic solvent in the external phase. The presence of organic solvent according to Hope increases the permeability of the membrane (without disrupting the liposomes) and when the organic solvent is diluted, the permeability decreases (note col. 7, lines 32-65; Examples and claims). What is lacking in Hope is the use of a cationic lipid and the teachings of the removal of the organic solvent.

Wheeler while disclosing liposomal formulations containing nucleic acids using ethanol in the method teaches that cationic lipids such as DOTAP and DOTMA are efficient carriers of negatively charged nucleic aids for transfection (note the abstract and col. 1, line 55 et seq, Examples and claims. Wheeler's compositions further include PEG derivatized phospholipids (col. 11, lines 28-32). Although Wheeler's method does

not involve using preformed liposomes, it is interesting to note Wheeler's teachings on col. 2, line 16 et seq., that loading of nucleic acids into preformed liposomes is practiced in the art. Wheeler's method involves similar procedure to the claimed method, except that the preformed liposomes are not used and the method of preparation involves the removal of ethanol by art known methods such as rotary evaporation (col. 18, line 40 through col. 19, line 12).

WO 98 while teaching compositions containing DOPAP, DSPC, and cholesterol teaches that PEG derivatized lipids provide steric stabilization and prevent the aggregation of the particles; WO therefore, includes PEG-lipids such as PEG-ceramides. The buffer used in the preparations is a citrate buffer (note the abstract, pages 17-19 and claims).

The use of cationic lipids in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Wheeler teaches that cationic lipids are efficient in transfecting cells with nucleic acids in a similar method of preparation involving ethanol. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Wheeler shows that the external ethanol can be removed by art known methods. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH.

The inclusion of PEG-lipids in the compositions of Hope would have been obvious to one of ordinary skill in the art since WO teaches their ability to provide steric stabilization. The use of citrate buffer would have been obvious to one of ordinary skill in the art since WO teaches it is a commonly used buffer in liposomal compositions.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants while admitting that like the present method, Hope deals with a

method of loading liposomes in the interior of the liposomes, but argue that on col. 10, lines 7-10 Hope specifically teaches that "generally, highly negatively charged species such as polynucleotides do not cross the liposomal membranes permeabilized by the solvent techniques disclosed herein"; applicants further point out col. 10, lines 10-13 of Hope wherein Hope states that this exclusion is so good that it can be used to entrap neutral species in the presence of charged species to accomplish a separation. This argument is not persuasive since Hope teaches on the same column following lines 10-13 that the charge on the molecule can be adjusted by several methods and in particular states "For example, charged oligonucleotides can be converted to less highly charged analogs which continue to display biological activity by methylation or conversion to the corresponding phosphorothioates, methylphosphonates and the like". Therefore, it is implicit from Hope's teachings that polynucleotides can also be loaded. The examiner also points out Hope's statements on col. 9: on line 53 et seq, Hope states "Unlike the ion gradient methods disclosed in the prior art, the solvent loading method is not limited to ionizable solutes". This statement clearly indicates that Hope's subsequent statements referred to by applicants pertain to his improvement over the prior art method whereby one can load even the neutral molecules. Furthermore, it should be pointed out that instant claims are not limited just to polynucleotides. Applicants argue that Hope is an inventor on both secondary references as well and thus, it may be presumed that he was fully aware of the formulations containing cationic liposomes at the time the Hope's patent was filed. This argument is not pertinent since the same rationale will be applicable since even Peter R. Cullis one of the inventors in instant application is also one of the inventors of patent 5,976,567 (wheeler) as well as the WO reference used in the combination.

Applicants' arguments on page 3, second paragraph are not found to be persuasive since as pointed out above, Hope's method pertains to both charged and neutral active agents and Wheeler's method is similar to instant method using cationic lipids and Wheeler's col. 2, line16 et seq., that loading of nucleic acids into preformed liposomes is practiced in the art.

Applicants' arguments on page 3, third paragraph are not found to be persuasive. Applicants argue that there is nothing in Hope indicates that aggregation is a problem. This argument is not found to be persuasive since WO teaches on page 17 that the presence of PEG-lipid improves the formulation process by reducing aggregation of the lipid particles during formation (goal is the same as in instant invention). This aggregation will be a problem whether recognized by Hope or not since Hope's invention also involves liposomes just as in instant invention and one of ordinary skill in the art would be motivated to include PEG lipid to prevent such a aggregation during formation. Furthermore, it is well recognized in the art that the presence of PEG-lipids in liposomal formulations would extend the blood circulation time of the liposomes (see below).

3. Claims 13-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hope (6,447,800) in view of Malone (PNAS, vol. 86, pp. 6077-6081, 1989) and Zalipsky (6,365,179).

As discussed above, Hope discloses a method of preparation of liposomes containing a variety of active agents. The method involves combining already formed liposomes with an active agent and organic solvent, ethanol (at least 10 %), allowing a certain amount of time and diluting the organic solvent in the external phase. The presence of organic solvent according to Hope increases the permeability of the membrane (without disrupting the liposomes) and when the organic solvent is diluted,

the permeability decreases (note col. 7, lines 32-65; Examples and claims). What is lacking in Hope is the use of a cationic lipid and the teachings of the removal of the organic solvent. What is also lacking in Hope is the use of a modified lipid such as PEG-phospholipid.

Malone teaches that the use of cationic liposomes containing DOTMA is an efficient way of RNA transfection (note the abstract and discussion).

Zalipsky while disclosing liposomal formulations teaches that modified lipids such as polymer derivatized lipids (PEG-phospholipids) extend the blood circulation time of the liposomes (col. 10, lines 28-37; col. 11, lines 12-57). The method of preparation in Zalipsky involves the use of ethanol and Zalipsky advocates the removal of ethanol by diafiltration (note Example 4 on col. 17).

The use of cationic lipid, DOTMA in the method of Hope, if the active agent involves a nucleic acid would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The removal of the already diluted ethanol in the external medium of Hope if it is deemed undesirable would have been obvious to one of ordinary skill in the art since Zalipski teaches that the external ethanol can be removed by diafiltration. The use of modified lipids in Hope would have been obvious to one of ordinary skill in the art since Zalipski also teaches that these lipids extend the circulation time of the liposomes. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants provide no specific arguments to this rejection except to state that the rejection is deficient for the same reasons as discussed above. Therefore, the same response as above is applicable.

4. Claims 13-20, and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable Schubert (Chemistry and Physics of Lipids, 58, 121-129, 1991) in view of Malone (PNAS, vol. 86, pp. 6077-6081, 1989) and either Zalipsky (6,365,179) or WO 98/51278 of record.

Schubert discloses a method of loading preformed liposomes by detergent-induced (destabilizing agent-induced) formation of transient membrane holes. The method involves the incubation of the preformed liposomes with the active agent such as nucleic acids and removal of the detergent (note the abstract and Materials and Method section). What is lacking in Schubert is the use of a cationic lipid. What is also lacking in Schubert is the use of a modified lipid such as PEG-phospholipid or PEG-ceramide.

Malone teaches that the use of cationic liposomes containing DOTMA is an efficient way of RNA transfection (note the abstract and discussion).

Zalipsky while disclosing liposomal formulations teaches that modified lipids such as polymer derivatized lipids (PEG-phospholipids) extend the blood circulation time of the liposomes (col. 10, lines 28-37; col. 11, lines 12-57).

As discussed above, WO 98 while teaching compositions containing DOPAP, DSPC, cholesterol teaches that PEG derivatized lipids provide steric stabilization and prevent the aggregation of the particles; WO therefore, includes PEG-lipids such as PEG-ceramides. The buffer used in the preparations is a citrate buffer (note the abstract, pages 17-19 and claims).

The use of cationic lipid, DOTMA in the method of Schubert would have been obvious to one of ordinary skill in the art since Malone teaches that this cationic lipid is efficient in transfecting cells with nucleic acids. The use of modified lipids in Schubert would have been obvious to one of ordinary skill in the art since Zalipski also teaches

that these lipids extend the circulation time of the liposomes or since WO 98 teaches their ability to sterically stabilize the particles. The criticality of citrate buffer is not readily apparent to the examiner since the selection of the buffer depends upon the desired pH; one of ordinary skill in the art would be motivated to use citrate buffer since WO teaches that it is commonly used in liposomal preparations containing nucleic acids.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that Schubert is substantially cumulative with Hope except that a different method for opening the membrane of preformed liposomes is disclosed. According to applicants, in Schubert, sodium cholate, a bile salt is used to open the membrane and that the examiner has not indicated why a person skilled in the art would anticipate that changing the liposome structure to include a cationic lipid would allow loading of pre-formed lipids with a negatively charged oligonucleotide, without this step of membrane opening being necessary. This argument is not found to be persuasive since according to Shubert, the bile acid (detergent) enables transient membrane holes; that means it perturbs the membrane without disrupting the vesicles just as in instant method and the rationale for one of ordinary skill in the art to use a cationic lipid has been clearly set forth by the examiner; that is, cationic lipids are efficient in transfecting cells with nucleic acids as taught by Malone.

5. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is 703 308 2440. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK